

Refine Search

Search Results -

Terms	Documents
L1 and mm2	1

Database:

US Pre-Grant Publication Full-Text Database
 US Patents Full-Text Database
 US OCR Full-Text Database
 EPO Abstracts Database
 JPO Abstracts Database
 Derwent World Patents Index
 IBM Technical Disclosure Bulletins

Search:

L5

Refine Search

Recall Text

Clear

Interrupt

Search History

DATE: Wednesday, July 14, 2004 [Printable Copy](#) [Create Case](#)

SetName Queryside by
sideHit
CountSet
Name
result set

DB=PGPB,USPT; PLUR=YES; OP=AND

L5 l1 and mm21 L5L4 l1 with l20 L4L3 l1 and L2160 L3L2 mm or mm2788077 L2L1 (adeno-associated adj virus or aav or raav) near7 (brain or cns or nervous
adj system or striatum or cerebrum or cerebellum or hippocampus)181 L1

END OF SEARCH HISTORY

[Generate Collection](#)[Print](#)**Search Results** - Record(s) 1 through 1 of 1 returned.

-
- ☐ 1. [20030216335](#). 27 Nov 02. 20 Nov 03. Method and reagent for the modulation of female reproductive diseases and conditions. Lockridge, Jennifer, et al. 514/44; A61K048/00.
-

[Generate Collection](#)[Print](#)

Terms	Documents
L1 and mm2	1

[Prev Page](#)[Next Page](#)[Go to Doc#](#)

09/887,854

=> s (adeno-associated(w)virus or aav or raav) (7a) (brain or cns or nervous(w) system or striatum or cerebrum or cerebellum or hippocampus)

L1 529 (ADENO-ASSOCIATED(W) VIRUS OR AAV OR RAAV) (7A) (BRAIN OR CNS OR NERVOUS(W) SYSTEM OR STRIATUM OR CEREBRUM OR CEREBELLUM OR HIPPO CAMPUS)

=> s mm or mm2

L2 1644646 MM OR MM2

=> s l1 and l2

L3 10 L1 AND L2

=> dup rem l3

PROCESSING COMPLETED FOR L3

L4 9 DUP REM L3 (1 DUPLICATE REMOVED)

=> d his

(FILE 'HOME' ENTERED AT 18:51:29 ON 14 JUL 2004)

FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH' ENTERED AT 18:52:17 ON 14 JUL 2004

L1 529 S (ADENO-ASSOCIATED(W)VIRUS OR AAV OR RAAV) (7A) (BRAIN OR CNS OR
L2 1644646 S MM OR MM2
L3 10 S L1 AND L2
L4 9 DUP REM L3 (1 DUPLICATE REMOVED)

=> d au ti so pi ab 1-9 14

L4 ANSWER 1 OF 9 MEDLINE on STN DUPLICATE 1
AU Hadaczek Piotr; Mirek Hanna; Bringas John; Cunningham Janet; Bankiewicz Krys
TI Basic fibroblast growth factor enhances transduction, distribution, and axonal transport of **adeno-associated virus** type 2 vector in rat **brain**.
SO Human gene therapy, (2004 May) 15 (5) 469-79.
Journal code: 9008950. ISSN: 1043-0342.
AB The ubiquitous expression of cell surface heparan sulfate proteoglycan, a binding receptor for adeno-associated virus type 2 (AAV-2), may account for the broad host range of this vector. Because the fibroblast growth factor receptor type 1 has been postulated to be a coreceptor for successful AAV-2 entry into host cells, we designed a strategy to investigate whether coadministration of this virus with basic fibroblast growth factor (bFGF) can enhance AAV-2-mediated gene delivery. We injected AAV-2-thymidine kinase (AAV-2-TK) vector into rat striata and checked whether coinjection with bFGF enhanced transduction and/or enlarged the area of transgene expression. Immunostaining confirmed the tropism of AAV-2-TK for neurons. The previous injection (7 days before vector delivery) of bFGF had no major impact on vector distribution area. However, when the vector was coinjected with bFGF, the right striatum showed an average viral transduction volume of 5 **mm**(3), which was more than 4-fold larger when compared with the left side (AAV-2-TK plus phosphate-buffered saline). This result clearly indicates that simultaneous injection of bFGF with AAV-2-TK can greatly enhance the volume of transduced tissue, probably by way of a competitive block of **AAV-2-binding** sites within the **striatum**. Robust TK immunoreactivity was also observed in the globus pallidus, which receives anterograde projections from the striatum. We propose that postsynaptic transport of recombinant particles was likely responsible for the distribution of TK in the globus pallidus on both bFGF-treated and untreated sides. In summary, we found that bFGF acts as an adjuvant for distribution of **AAV-2** in rat **brain**.

L4 ANSWER 2 OF 9 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

- AU Sanftner L M (Reprint); Suzuki B M; Doroudchi M M; Feng L; McClelland A; Forsayeth J R; Cunningham J
- TI Striatal delivery of rAAV-hAADC to rats with preexisting immunity to AAV
- SO MOLECULAR THERAPY, (MAR 2004) Vol. 9, No. 3, pp. 403-409.
 Publisher: ACADEMIC PRESS INC ELSEVIER SCIENCE, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495 USA.
 ISSN: 1525-0016.
- AB We tested the hypotheses that initial immunization of rats with rAAV might limit subsequent transduction by **rAAV-hAADC** when stereotactically infused into the **striatum** and that the level of inhibition would correlate with AAV neutralizing antibody titers. Immunohistochemical detection of AADC and analysis by stereology revealed that the control group (no immunization) had the greatest volume of distribution of AADC ($20.32 \pm 2.03 \text{ mm}^3$) (\pm SD). There was a 58% decrease in spread ($8.46 \pm 3.67 \text{ mm}^3$, $P < 0.008$) in the high-dose immunization group (5×10^{10} vg rAAV-null). Transduction weakly correlated with preexisting titer levels of neutralizing antibody at the time of intrastriatal rAAV-hAADC infusion. Only rats with neutralizing antibody titers of 1: 1208 332 had significantly decreased AADC transgene expression compared to the unimmunized control group. Immunohistochemistry on serial sections for inflammatory markers including CFAP, CD11b, CD4, and CD8a revealed normal morphology and no cellular infiltration, suggesting little immune reaction in the **CNS**. We conclude that **rAAV** vectors can transduce **brain** tissue in the context of preexisting immunity, but that efficiency of transduction declines significantly in the presence of very high titers of neutralizing antibodies. These results have important implications for gene therapy for CNS disorders.
- L4 ANSWER 3 OF 9 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
- AU Xu, Y. [Reprint Author]; Wang, L.; Uy, M. I.; Li, J.; Wang, B.; Zhou, L.; Xiao, X.
- TI Widespread gene delivery and expression in adult mouse **brain** by recombinant **adeno - associated virus** for potential gene therapy of ischemic injuries in selective vulnerable regions.
- SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. 861.9. <http://sfn.scholarone.com>. e-file. Meeting Info.: 33rd Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 08-12, 2003. Society of Neuroscience.
- AB Many disseminated neurological disorders are potentially manageable by gene therapy. Widespread somatic gene transfer in adult CNS by systemic delivery and without irradiation has not been documented. We report here the successful use of recombinant adeno-associated virus serotype-5 (rAAV5) vectors for widespread delivery of the beta-galactosidase (beta-gal) reporter expression cassette and brain-derived neurotrophic factor (BDNF) into the adult mouse brain. Intraventricular microinjection was performed using a microprocessor-driven syringe pump at a rate comparable to the flow of the cerebral spinal fluid. Nine to 35 days after injection, widespread beta-gal expression can be found in the hippocampal CA1, CA3, dentate gyrus, subventricular zone, indusium griseum, lateral entorhinal cortex, and septal regions. The beta-gal positive cells were detected in a wide span of 5.74 mm in the rostral-caudal direction. The pattern of BDNF expression is very similar. A slight shift of the injection site to the more posterior location extended the transgene expression to thalamus, hypothalamus, and dorsal lateral geniculate regions. Quantitative analysis suggests that the percentage of the infected cells varies with brain regions and anatomic structures. Immunohistostaining and co-localization show that most of the positively stained cells are neurons. We conclude that 1) widespread gene delivery to the central nervous system is possible with rAAV5; 2) the transgene expressions are predominantly in neurons; 3) the transgene distribution pattern depends on the injection site; and 4) there is a significant level of expression in the contralateral side of the

injection, suggesting a transgene migration to locations remote from the injection site.

- L4 ANSWER 4 OF 9 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AU Richichi, C. [Reprint Author]; Lin, D. E.; Moneta, D. [Reprint Author];
Colella, D. [Reprint Author]; Aliprandi, M. [Reprint Author]; Stefanin, D.
[Reprint Author]; Grignaschi, G. [Reprint Author]; Zennaro, E. [Reprint
TI Author]; Vezzani, A. [Reprint Author]; During, M. J.
ADENO - ASSOCIATED VIRAL VECTOR (RAAV) CARRYING THE NEUROPEPTIDE Y GENE
INDUCES LONG - LASTING PEPTIDE TRANSDUCTION IN RAT HIPPOCAMPUS AND
INHIBITS LIMBIC SEIZURES.
SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002)
Vol. 2002, pp. Abstract No. 603.12. <http://sfn.scholarone.com>. cd-rom.
Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience.
Orlando, Florida, USA. November 02-07, 2002. Society for Neuroscience.
AB We investigated the effect of NPY overexpression in the rat
hippocampus on limbic seizures using an **rAAV** vector
carrying the NPY gene (2 l AAV-NPY, 4.2x10⁸). Transgene expression was
maximal 4 weeks after its intrahippocampal delivery and lasted for about 6
months, as assessed by in situ hybridization analysis of NPY mRNA and
peptide immunostaining. NPY specifically increased in hilar interneurons
and their axonal projections. Immunofluorescence using green fluorescence
protein as a reporter gene, showed that the rAAV spreads for about 2
mm from its injection site. Rats injected 2.5 months before with
rAAV-NPY both in septal and temporal poles of the hippocampus bilaterally
had less EEG seizures induced by intrahippocampal injection of 40 ng
kainic acid. Thus, the number of seizures (25.5, n=5) and the duration of
seizures (24.5 3.2 min) in AAV-empty cassette injected rats was reduced by
2-fold on average (p<0.01). After intracerebroventricular injection of
250 ng kainic acid, only the onset of EEG seizures was significantly
delayed by 2-fold (p<0.01) in rats pre-injected with rAAV-NPY as before.
Thus, rAAV mediated long-term transduction of NPY into hilar interneurons
inhibits seizures or delays their onset depending on their way of
induction. This suggests that chronic increase of an inhibitory peptide
in crucial brain sites may represent a novel strategy for antiepileptic
treatment.
- L4 ANSWER 5 OF 9 MEDLINE on STN
AU During M J; Kaplitt M G; Stern M B; Eidelberg D
TI Subthalamic GAD gene transfer in Parkinson disease patients who are
candidates for deep brain stimulation.
SO Human gene therapy, (2001 Aug 10) 12 (12) 1589-91.
Journal code: 9008950. ISSN: 1043-0342.
AB This gene transfer experiment is the first Parkinson's Disease (PD)
protocol to be submitted to the Recombinant DNA Advisory Committee. The
principal investigators have uniquely focused their careers on both
pre-clinical work on gene transfer in the brain and clinical expertise in
management and surgical treatment of patients with PD. They have
extensively used rodent models of PD for proof-of-principle experiments on
the utility of different vector systems. PD is an excellent target for
gene therapy, because it is a complex acquired disease of unknown etiology
(apart from some rare familial cases) yet it is characterized by a
specific neuroanatomical pathology, the degeneration of dopamine neurons
of the substantia nigra (SN) with loss of dopamine input to the striatum.
This pathology results in focal changes in the function of several deep
brain nuclei, which have been well-characterized in humans and animal
models and which account for many of the motor symptoms of PD. Our
original approaches, largely to validate in vivo gene transfer in the
brain, were designed to facilitate dopamine transmission in the
striatum using an **AAV** vector expressing
dopamine-synthetic enzymes. Although these confirmed the safety and
potential efficacy of AAV, complex patient responses to dopamine
augmenting medication as well as poor results and complications of human
transplant studies suggested that this would be a difficult and

potentially dangerous clinical strategy using current approaches. Subsequently, we and others investigated the use of growth factors, including GDNF. These showed some encouraging effects on dopamine neuron survival and regeneration in both rodent and primate models; however, uncertain consequences of long-term growth factor expression and question regarding timing of therapy in the disease course must be resolved before any clinical study can be contemplated. We now propose to infuse into the subthalamic nucleus (STN) recombinant AAV vectors expressing the two isoforms of the enzyme glutamic acid decarboxylase (GAD-65 and GAD-67), which synthesizes the major inhibitory neurotransmitter in the brain, GABA. The STN is a very small nucleus (140 cubic ~~mm~~ or 0.02% of the total brain volume, consisting of approximately 300,000 neurons) which is disinhibited in PD, leading to pathological excitation of its targets, the internal segment of the globus pallidus (GPi) and substantia nigra pars reticulata (SNpr). Increased GPi/SNpr outflow is believed responsible for many of the cardinal symptoms of PD, i.e., tremor, rigidity, bradykinesia, and gait disturbance. A large amount of data based on lesioning, electrical stimulation, and local drug infusion studies with GABA-agonists in human PD patients have reinforced this circuit model of PD and the central role of the STN. Moreover, the closest conventional surgical intervention to our proposal, deep brain stimulation (DBS) of the STN, has shown remarkable efficacy in even late stage PD, unlike the early failures associated with recombinant GDNF infusion or cell transplantation approaches in PD. We believe that our gene transfer strategy will not only palliate symptoms by inhibiting STN activity, as with DBS, but we also have evidence that the vector converts excitatory STN projections to inhibitory projections. This additional dampening of outflow GPi/SNpr outflow may provide an additional advantage over DBS. Moreover, of perhaps the greatest interest, our preclinical data suggests that this strategy may also be neuroprotective, so this therapy may slow the degeneration of dopaminergic neurons. We will use both GAD isoforms since both are typically expressed in inhibitory neurons in the brain, and our data suggest that the combination of both isoforms is likely to be most beneficial. Our preclinical data includes three model systems: (1) old, chronically lesioned parkinsonian rats in which intraSTN GAD gene transfer results not only in improvement in both drug-induced asymmetrical behavior (apomorphine symmetrical rotations), but also in spontaneous behaviors. In our second model, GAD gene transfer precedes the generation of a dopamine lesion. Here GAD gene transfer showed remarkable neuroprotection. Finally, we carried out a study where GAD-65 and GAD-67 were used separately in monkeys that were resistant to MPTP lesioning and hence showed minimal symptomatology. Nevertheless GAD gene transfer showed no adverse effects and small improvements in both Parkinson rating scales and activity measures were obtained. In the proposed clinical trial, all patients will have met criteria for and will have given consent for STN DBS elective surgery. Twenty patients will all receive DBS electrodes, but in addition they will be randomized into two groups, to receive either a solution containing rAAV-GAD, or a solution which consists just of the vector vehicle, physiological saline. Patients, care providers, and physicians will be blind as to which solution any one patient receives. All patients, regardless of group, will agree to not have the DBS activated until the completion and unblinding of the study. Patients will be assessed with a core clinical assessment program modeled on the CAPSIT, and in addition will also undergo a preop and several postop PET scans. At the conclusion of the study, if any patient with sufficient symptomatic improvement will be offered DBS removal if they so desire. Any patients with no benefit will simply have their stimulators activated, which would normally be appropriate therapy for them and which requires no additional operations. If any unforeseen symptoms occur from STN production of GABA, this might be controlled by blocking STN GABA release with DBS, or STN lesioning could be performed using the DBS electrode. Again, this treatment would not subject the patient to additional invasive brain surgery. The trial described here reflects an evolution in our thinking about the best

strategy to make a positive impact in Parkinson Disease by minimizing risk and maximizing potential benefit. To our knowledge, this proposal represents the first truly blinded, completely controlled gene or cell therapy study in the brain, which still provides the patient with the same surgical procedure which they would normally receive and should not subject the patient to additional surgical procedures regardless of the success or failure of the study. This study first and foremost aims to maximally serve the safety interests of the individual patient while simultaneously serving the public interest in rigorously determining in a scientific fashion if gene therapy can be effective to any degree in treating Parkinson's disease.

- L4 ANSWER 6 OF 9 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
AU Cunningham J; Oiwa Y; Nagy D; Podsakoff G; Colosi P; Bankiewicz K S
(Reprint)
TI Distribution of AAV-TK following intracranial convection-enhanced delivery
into rats
SO CELL TRANSPLANTATION, (SEP-OCT 2000) Vol. 9, No. 5, pp. 585-594.
Publisher: COGNIZANT COMMUNICATION CORP, 3 HARTSDALE ROAD, ELMSFORD, NY
10523-3701.
ISSN: 0963-6897.
- AB Adeno-associated virus (AAV)-based vectors are being tested in animal models as viable treatments for glioma and neurodegenerative disease and could potentially be employed to target a variety of central nervous system disorders. The relationship between dose of injected vector and its resulting distribution in brain tissue has not been previously reported nor has the most efficient method of delivery been determined. Hen we report that convection-enhanced delivery (CED) of 2.5×10^8 , 2.5×10^9 , or 2.5×10^{10} particles of **AAV**-thymidine kinase (**AAV-TK**) into rat **brain** revealed a clear dose response. In the high-dose group, a volume of 300 μm^3 of brain tissue was partially transduced. Results showed that infusion pump and subcutaneous osmotic pumps were both capable of delivering vector via CED and that total particle number was the most important determining factor in obtaining efficient expression. Results further showed differences in histopathology between the delivery groups. While administration of vector using infusion pump had relatively benign effects, the use of osmotic pumps resulted in notable toxicity to the surrounding brain tissue. To determine tissue distribution of vector following intracranial delivery, PCR analysis was performed on tissues from rats that received high doses of AAV-TK. three weeks following CED, vector could be detected in both hemispheres of the brain, spinal cord, spleen, and kidney.
- ✓ L4 ANSWER 7 OF 9 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AU Passini, M. A. [Reprint author]; Lee, E. B.; Crystal, A.; Wolfe, J. H.
TI The human B-glucuronidase promoter provides long-term expression from an adeno-associated viral vector following in vivo injections of multiple brain structures.
SO Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-668.8. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 04-09, 2000. Society for Neuroscience.
ISSN: 0190-5295.
- AB The site and duration of gene expression from adeno-associated virus (AAV) vectors vary in different regions of the adult mouse brain. This observation may be a result of differences in the ability of specific brain regions to utilize the promoter driving gene expression. Thus, we analyzed the behavior of an AAV vector under the control of an ubiquitously expressed CNS promoter to understand its potential as a long-term global expresser of exogenous genes. An AAV construct containing the human B-Glucuronidase (GUSB) promoter upstream of the human GUSB cDNA was engineered and injected into multiple brain regions in adult mice. Strong mRNA expression and enzyme activity were detected 3-5 months after viral administration in the cortex, hippocampus, subiculum,

striatum, substantia nigra, hypothalamus, thalamus, and cerebellum. Transduced cells, as determined by in situ hybridization, remained confined to the injection site. However, when analyzing exogenous enzyme activity, cells were detected in the in situ positive regions and in areas located 3 mm away from the injection site. A feature of GUSB and most other lysosomal storage enzymes is that they can be secreted by normal cells and taken up by mutant cells in a process called cross correction. This data demonstrates that a single administration of AAV in the brain can lead to widespread enzyme delivery, and that differences in AAV vector expression exists in different structures of the adult mouse brain.

- L4 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2004 ACS on STN
 AU Mandel, R. J.; Rendahl, K. G.; Spratt, S. K.; Snyder, R. O.; Cohen, L. K.; Leff, S. E.
 TI Characterization of intrastriatal recombinant adeno-associated virus-mediated gene transfer of human tyrosine hydroxylase and human GTP-cyclohydrolase I in a rat model of Parkinson's disease
 SO Journal of Neuroscience (1998), 18(11), 4271-4284
 CODEN: JNRSDS; ISSN: 0270-6474
 AB To achieve local, continuous L-DOPA delivery in the striatum by gene replacement as a model for a gene therapy for Parkinson's disease, the present studies used high titer purified recombinant adeno-associated virus (rAAV) containing cDNAs encoding human tyrosine hydroxylase (hTH) or human GTP-cyclohydrolase I [GTPCHI, the rate-limiting enzyme for tetrahydrobiopterin (BH4) synthesis] or both to infect the 6-OHDA denervated rat striatum. Striatal TH and GTPCHI staining was observed 3 wk after rAAV transduction, with little detectable perturbation of the tissue. Six months after intrastriatal rAAV transduction, TH staining was present but apparently reduced compared with the 3 wk survival time. In a sep. group of animals, striatal TH staining was demonstrated 1 yr after rAAV transduction. Double staining studies using the neuronal marker NeuN indicated that >90% of rAAV-transduced cells expressing hTH were neurons. Microdialysis expts. indicated that only those lesioned animals that received the mixture of MD-TH and MD-GTPCHI vector displayed BH4 independent in vivo L-DOPA production (mean .apprx.4-7 ng/mL). Rats that received the hTH rAAV vector alone produced measurable L-DOPA (mean .apprx.1-4 ng/mL) only after receiving exogenous BH4. L-Aromatic amino acid decarboxylase blockade, but not 100 mM KCl-induced depolarization, enhanced L-DOPA overflow, and animals in the non-hTH groups (GTPCHI and alkaline phosphatase) yielded minimal L-DOPA. Although elevated L-DOPA was observed in animals that received mixed hTH and hGTPCHI rAAV vectors, there was no reduction of apomorphine-induced rotational behavior 3 wk after intrastriatal vector injection. These data demonstrate that purified rAAV, a safe and nonpathogenic viral vector, mediates long-term striatal hTH transgene expression in neurons and can be used to successfully deliver L-DOPA to the striatum.
- L4 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2004 ACS on STN
 AU Okada, H.; Miyamura, K.; Itoh, T.; Hagiwara, M.; Wakabayashi, T.; Mizuno, M.; Colosi, P.; Kurtzman, G.; Yoshida, J.
 TI Gene therapy against an experimental glioma using adeno-associated virus vectors
 SO Gene Therapy (1996), 3(11), 957-964
 CODEN: GETHEC; ISSN: 0969-7128
 AB The efficacy of gene therapy for glioma was examined using adeno-associated virus (AAV)-based vectors to deliver genes to exptl. tumors in mice. Stereotactic injection of 2+105 U-251SP human glioma cells into the brains of nude mice produced tumors of 19.06 ± 1.79 mm² 17 days after injection. Employing a high titer preparation of AAV vector containing the gene for β-galactosidase (AAV-lacZ), dose-dependent transduction of U-251SP cells was seen in vitro. When 1.6 × 10¹⁰ AAV-lacZ particles were directly injected into tumors in vivo, 30-40% of the cells

along the needle track expressed β -galactosidase. Transduction of U-251SP cells in vitro with an AAV vector containing a bicistronic gene encoding both herpes simplex thymidine kinase and human interleukin-2 (AAV-tk-IRES-IL2) rendered them sensitive to the cytotoxic effects of ganciclovir (GCV) and IL-2 was produced in a dose-dependent manner. Cocultures of AAV-tk-IRES-IL2 transduced cells and nontransduced cells proved highly sensitive to GCV indicating the contribution of the bystander effect. Stereotactic delivery of 6×10^{10} AAV-tk-IRES-IL2 particles into day 7 tumors in nude mice followed by administration of GCV for 6 days, resulted in a 35-fold reduction in the mean volume of tumors compared with controls. Normal brains did not suffer from any toxic effect of the administration of AAV-tk-IRES-IL2 and GCV. These results indicate that high titer AAV vector treatment may be safe and effective for in vivo gene therapy of human brain tumors.

=>

09/887,854

=> d his

(FILE 'HOME' ENTERED AT 11:17:27 ON 14 MAY 2004)

FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH' ENTERED AT 11:17:59 ON 14 MAY 2004

L1 16660 S (INFUSION OR OSMOTIC) (3A) PUMP
L2 10034 S ADENO-ASSOCIATED(W) (VIRUS OR VIRAL)
L3 15 S L1 AND L2
L4 11 DUP REM L3 (4 DUPLICATES REMOVED)

=> d bib ab 1-11 14

L4 ANSWER 1 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:173806 CAPLUS
DN 138:180748
TI Use of **adeno-associated virus** vectors for
delivery of mammalian glial-derived neurotrophic factor genes for treatment
of neurodegenerative diseases
IN Ozawa, Keiya; Muramatsu, Shin-ichi
PA Ikeguchi, Kunihiro, Japan; Nakano, Imaharu
SO PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003018821	A2	20030306	WO 2002-JP8761	20020829
	WO 2003018821	A3	20031030		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
	US 2003050273	A1	20030313	US 2002-230875	20020828
PRAI	US 2001-315838P	P	20010829		
AB	Compns. and methods for treating subjects with preexisting neuronal damage are disclosed. The compns. and methods use adeno-assocd . virus (AAV)-based gene delivery systems for delivering glial cell line-derived neurotrophic factor (GDNF) to subjects with neurodegenerative conditions such as Parkinson's disease.				

L4 ANSWER 2 OF 11 MEDLINE on STN
AN 2003545726 MEDLINE
DN PubMed ID: 14625141
TI Brain-derived neurotrophic factor in the ventral midbrain-nucleus accumbens pathway: a role in depression.
AU Eisch Amelia J; Bolanos Carlos A; de Wit Joris; Simonak Ryan D; Pudiak Cindy M; Barrot Michel; Verhaagen Joost; Nestler Eric J
CS Department of Psychiatry, The University of Texas Southwestern Medical Center, Texas, Dallas 75390-9070, USA.
SO Biological psychiatry, (2003 Nov 15) 54 (10) 994-1005.
Journal code: 0213264. ISSN: 0006-3223.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English

FS Priority Journals
 EM 200312
 ED Entered STN: 20031120
 Last Updated on STN: 20031230
 Entered Medline: 20031229
 AB BACKGROUND: Previous work has shown that brain-derived neurotrophic factor (BDNF) and its receptor, tyrosine kinase receptor B (TrkB), are involved in appetitive behavior. Here we show that BDNF in the ventral tegmental area-nucleus accumbens (VTA-NAc) pathway is also involved in the development of a depression-like phenotype. METHODS: Brain-derived neurotrophic factor signaling in the VTA-NAc pathway was altered in two complementary ways. One group of rats received intra-VTA infusion of vehicle or BDNF for 1 week. A second group of rats received intra-NAc injections of vehicle or **adeno-associated viral** vectors encoding full-length (TrkB.FL) or truncated (TrkB.T1) TrkB; the latter is kinase deficient and serves as a dominant-negative receptor. Rats were examined in the forced swim test and other behavioral tests. RESULTS: Intra-VTA infusions of BDNF resulted in 57% shorter latency to immobility relative to control animals, a depression-like effect. Intra-NAc injections of TrkB.T1 resulted in and almost fivefold longer latency to immobility relative to TrkB.FL and control animals, an antidepressant-like effect. No effect on anxiety-like behaviors or locomotion was seen. CONCLUSIONS: These data suggest that BDNF action in the VTA-NAc pathway might be related to development of a depression-like phenotype. This interpretation is intriguing in that it suggests a role for BDNF in the VTA-NAc that is opposite of the proposed role for BDNF in the hippocampus.

L4 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
 AN 2002:52003 CAPLUS
 DN 136:117371
 TI Method of inducing an immunological CTL response by lymphatic system delivery of peptide vaccine
 IN Kundig, Thomas M.; Simard, John J. L.
 PA Switz.
 SO U.S. Pat. Appl. Publ., 48 pp., Cont.-in-part of U. S. Ser. No. 380,534.
 CODEN: USXXCO

DT Patent
 LA English

FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002007173	A1	20020117	US 2001-776232	20010202
	WO 9902183	A2	19990121	WO 1998-US14289	19980710
	WO 9902183	A3	19990514		
	W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	AU 2001097432	A5	20020808	AU 2001-97432	20011221
	WO 2002062368	A2	20020815	WO 2002-US2033	20020122
	WO 2002062368	A3	20030925		
	WO 2002062368	C1	20031120		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,			

CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003138808 A1 20030724 US 2002-225568 20020820
 PRAI CA 1997-2209815 A 19970710
 US 1997-988320 B2 19971210
 WO 1998-US14289 W 19980710
 US 1999-380534 A2 19990901
 US 1998-26066 A2 19980219
 US 2000-561572 A2 20000428
 US 2000-715835 A2 20001116
 US 2001-776232 A 20010202
 US 2001-336968P P 20011107
 US 2001-337017P P 20011107
 US 2002-363210P P 20020307
 US 2002-117937 A2 20020404
 AB Disclosed herein are methods for inducing an immunol. CTL response to an antigen by sustained, regular delivery of the antigen to a mammal so that the antigen reaches the lymphatic system. Antigen is delivered at a level sufficient to induce an immunol. CTL response in a mammal and the level of the antigen in the mammal's lymphatic system is maintained over time sufficient to maintain the immunol. CTL response. Also disclosed is an article of manufacture for delivering an antigen that induces a CTL response in an animal. The antigen can be used in vaccines for cancer or infection.

L4 ANSWER 4 OF 11 MEDLINE on STN DUPLICATE 1
 AN 2002404319 MEDLINE
 DN PubMed ID: 12153331
 TI Potential new methods for antiepileptic drug delivery.
 AU Fisher Robert S; Ho Jet
 CS Stanford Comprehensive Epilepsy Center, Stanford University Medical Center, Stanford, California 94305-5235, USA.. rfisher@stanford.edu
 SO CNS drugs, (2002) 16 (9) 579-93. Ref: 125
 Journal code: 9431220. ISSN: 1172-7047.
 CY New Zealand
 DT Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
 LA English
 FS Priority Journals
 EM 200210
 ED Entered STN: 20020803
 Last Updated on STN: 20021017
 Entered Medline: 20021016
 AB Use of novel drug delivery methods could enhance the efficacy and reduce the toxicity of antiepileptic drugs (AEDs). Slow-release oral forms of medication or depot drugs such as skin patches might improve compliance and therefore seizure control. In emergency situations, administration via rectal, nasal or buccal mucosa can deliver the drug more quickly than can oral administration. Slow-release oral forms and rectal forms of AEDs are already approved for use, nasal and buccal administration is currently off-label and skin patches for AEDs are an attractive but currently hypothetical option. Therapies under development may result in the delivery of AEDs directly to the regions of the brain involved in seizures. Experimental protocols are underway to allow continuous infusion of potent excitatory amino acid antagonists into the CSF. In experiments with animal models of epilepsy, AEDs have been delivered successfully to seizure foci in the brain by programmed **infusion pumps**, acting in response to computerised EEG seizure detection. Inactive prodrugs can be given systemically and activated at the site of the seizure focus by locally released compounds. One such drug under development is DP-VPA (or DP16), which is cleaved to valproic acid (sodium valproate) by phospholipases at the seizure focus. Liposomes and nanoparticles are engineered micro-reservoirs of a drug, with attached antibodies or receptor-specific binding agents designed to target the

particles to a specific region of the body. Liposomes in theory could deliver a high concentration of an AED to a seizure focus. Penetration of the blood-brain barrier can be accomplished by linking large particles to iron transferrin or biological toxins that can cross the barrier. In the near future, it is likely that cell transplants that generate neurotransmitters and neuromodulators will accomplish renewable endogenous drug delivery. However, the survival and viability of transplanted cells have yet to be demonstrated in the clinical setting. Gene therapy also may play a role in local drug delivery with the use of adenovirus, **adeno-associated virus**, herpesvirus or other delivery vectors to induce brain cells to produce local modulatory substances. New delivery systems should significantly improve the therapeutic/toxic ratio of AEDs.

L4 ANSWER 5 OF 11 MEDLINE on STN
 AN 2002453940 MEDLINE
 DN PubMed ID: 12208666
 TI Peripheral but not central leptin prevents the immunosuppression associated with hypoleptinemia in rats.
 AU Zhang Y; Wilsey J T; Frase C D; Matheny M M; Bender B S; Zolotukhin S; Scarpace P J
 CS Geriatric Research, Education and Clinical Center, Department of Veterans Affairs Medical Center, Gainesville, FL 32608-1197 USA.
 NC AG 17047 (NIA)
 SO Journal of endocrinology, (2002 Sep) 174 (3) 455-61.
 Journal code: 0375363. ISSN: 0022-0795.
 CY England: United Kingdom
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 200211
 ED Entered STN: 20020906
 Last Updated on STN: 20021212
 Entered Medline: 20021108
 AB Leptin is a peripheral immunoenhancing reagent that directly activates splenic lymphocytes in mice. We found that a 48 h fast in rats resulted in a decrease in serum leptin that was accompanied by a lower delayed-type hypersensitivity (DTH) response. Peripheral leptin replacement completely restored this response in fasted animals. We employed a recombinant **adeno-associated virus** (rAAV) system to deliver leptin gene directly into rat brain to assess the effect of sustained long-term central expression of leptin on immune responses. The rAAV-leptin rats had elevated central leptin over the 60 day duration of the experiment, whereas body fat and circulating leptin fell to near zero levels. The DTH response was significantly reduced by 10-20% in rats receiving rAAV-leptin compared with the control rats, and the difference was maintained for over 50 h. When the rats undergoing rAAV-leptin gene therapy were given either murine recombinant leptin or PBS s.c., rats receiving leptin had a 17% higher DTH response than rats receiving PBS. The isolated splenocytes from the former group also proliferated 34% more in vitro in response to the mitogen concanavalin A as compared with the latter group. These results suggest that peripheral leptin has a dominant role in maintaining T-cell-mediated immune responses in rats, and central leptin is unable to compensate for the immunosuppression associated with peripheral hypoleptinemia. Furthermore, preservation of normal cell-mediated immune responses does not require fat tissue as long as serum leptin levels are maintained.

L4 ANSWER 6 OF 11 MEDLINE on STN
 AN 2002631711 MEDLINE
 DN PubMed ID: 12389290
 TI Gene therapy for spinal applications.
 AU Hidaka Chisa; Khan Safdar N; Farmer James C; Sandhu Harvinder S
 CS Hospital for Special Surgery, Belfer Gene Therapy Core Facility, Weill

SO Medical College of Cornell University, New York, NY, USA.. hidakac@hss.edu
 Orthopedic clinics of North America, (2002 Apr) 33 (2) 439-46. Ref: 76
 Journal code: 0254463. ISSN: 0030-5898.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
 LA English
 FS Abridged Index Medicus Journals; Priority Journals
 EM 200211
 ED Entered STN: 20021023
 Last Updated on STN: 20021213
 Entered Medline: 20021106
 AB Gene therapy is a promising drug delivery mechanism for the treatment of spinal disorders. Currently, the technique has been most useful in enhancing growth factor therapy for spinal fusion, intervertebral disc regeneration, and spinal cord injury healing. Gene therapy allows for the high-level local production of growth factors, obviating the need for slow release carriers or continuous **infusion pumps** that are otherwise necessary because of the short half-lives of most peptide growth factors. Although continuous expression is desirable, growth factor therapy is usually intended to be transient. The typical expression profile of Ad vectors--at a high level over 2 weeks or so--has been ideal, leading to its widespread use in these applications. Despite the ability of Ad to deliver genes directly in vivo, however, the cell-based ex vivo approach has been used widely in spinal applications. In spinal cord injury, cells such as peripheral nerve or Schwann cells may provide a permissive substrate for axonal growth [51]. For spinal fusion and IVD regeneration, ex vivo manipulation of cells facilitates gene transfer, because bone and IVD tissue are too dense to be penetrated by injection of Ad or other vectors. The use of cells may be advantageous in these applications in which new tissue formation is the goal. Finally, the use of genetically modified cells may decrease the inflammatory reaction induced by Ad vectors. Although gene therapy for spinal disorders has been centered around Ad-mediated transfer of single growth factor genes, the options for candidate genes and vectors are growing rapidly. Ad vectors are being improved by decreasing their immunogenicity and altering their tropism [2]. Vectors based on other viruses (such as herpes, **adeno-associated virus**, and lentivirus) are being developed, also with lower immunogenicity and with longer durations of expression [26,67]. Regulated expression, such as with the tetracycline regulated promoter, is being developed so that genes can be turned on or off as needed. Such regulation may be sensitive even to physiologic cues in the future [68,69]. Finally, the high throughput technologies, such as the gene chip, are elucidating thousands of genes that may be good candidates for the enhancement of bone healing and IVD and spinal cord regeneration. Genes whose products not only support bone, fibrocartilage, or axon growth but also neutralize natural inhibitors or promote tissue remodeling and maturation may be good future candidates. In the future, a series of vectors with multiple genes that are regulated by physiologic cues might be used to enhance spinal fusion, restore IVD tissue, or support spinal cord healing.

L4 ANSWER 7 OF 11 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
 AN 2002:520392 SCISEARCH
 GA The Genuine Article (R) Number: 566BZ
 TI Current issues in cochlear gene transfer
 AU Lalwani A K (Reprint); Jero J; Mhatre A N
 CS Univ Calif San Francisco, Dept Otolaryngol Head & Neck Surg, Epstein Labs, Lab Mol Otol, 533 Parnassus Ave, U490A, San Francisco, CA 94143 USA (Reprint); Univ Calif San Francisco, Dept Otolaryngol Head & Neck Surg, Epstein Labs, Lab Mol Otol, San Francisco, CA 94143 USA; Univ Calif San Francisco, Dept Otolaryngol Head & Neck Surg, Div Otol Neurotol & Skull Base Surg, San Francisco, CA 94143 USA; Univ Helsinki, Cent Hosp, Dept

Otolaryngol, FIN-00290 Helsinki, Finland
CYA USA; Finland
SO AUDIOLOGY AND NEURO-OTOLOGY, (MAY-JUN 2002) Vol. 7, No. 3, pp. 146-151.
Publisher: KARGER, ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND.
ISSN: 1420-3030.

DT Article; Journal

LA English

REC Reference Count: 20

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Cochlear gene therapy represents a potential experimental and therapeutic tool to understand and treat deafness. In designing cochlear gene transfer studies, the chosen route of delivery of vector and the choice of gene therapy vector have to be given careful consideration. Several different routes of delivery have been tested in our laboratory including **infusion** with **osmotic mini-pump**, direct microinjection into the cochlea and application of vector-transgene complex-soaked Gelfoam into the direct contact with the round window membrane. In our experience, the latter is an easy, safe and atraumatic technique to deliver gene into the cochlea. A number of different gene transfer vectors have been investigated in vivo for their efficacy, utility and safety in intracochlear gene transfer. Vectors successfully studied include cationic liposomes, **adeno-associated virus**, adenovirus, lentivirus, herpes simplex virus and vaccinia virus. While the viral vectors offer clear experimental advantages, human gene therapy in the future will likely utilize nonviral vectors to maximize safety. Finally, safety issues regarding dissemination of gene transfer vectors beyond the target cochlea will need to be adequately addressed. Copyright (C) 2002 S. KargerAG, Basel.

L4 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN

AN 2001:844926 CAPLUS

DN 135:366764

TI Method of controlling L-dopa production and of treating dopamine deficiency

IN Mandel, Ronald J.; Leff, Stuart E.

PA Cell Genesys, Inc., USA

SO U.S., 13 pp.
CODEN: USXXAM

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6319905	B1	20011120	US 1999-314790	19990519
PRAI	US 1998-114016P	P	19981229		

AB The present invention provides an effective approach to achieve the tightly modulated production of L-DOPA and/or dopamine at a preselected target location in the brain of a mammal by combining gene therapy approaches to supply a key enzyme in the synthesis of L-DOPA such as tyrosine hydroxylase, and novel drug delivery modalities to administer a uniform level of a modulator of the activity of such key enzyme. The fine-tuned administration of the modulator establishes continuously uniform levels of modulator which in turn allow the effective modulation of L-DOPA and/or dopamine levels at a preselected target location in the brain of the mammal.

RE.CNT 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 11 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

AN 2002:22879 BIOSIS

DN PREV200200022879

TI **Adeno-associated viral** delivery of GDNF
protects striatal neurons in a rat model of Huntington's Disease.

AU McBride, J. L. [Reprint author]; Chen, E. Y. [Reprint author]; Leventhal,

L. [Reprint author]; During, M. J.; Kordower, J. H. [Reprint author]
 CS Neurological Sciences, Rush-Presbyterian, St Luke's Med Ctr, Chicago, IL, USA
 SO Society for Neuroscience Abstracts, (2001) Vol. 27, No. 2, pp. 2574. print.
 Meeting Info.: 31st Annual Meeting of the Society for Neuroscience. San Diego, California, USA. November 10-15, 2001.
 ISSN: 0190-5295.
 DT Conference; (Meeting)
 Conference; Abstract; (Meeting Abstract)
 LA English
 ED Entered STN: 26 Dec 2001
 Last Updated on STN: 25 Feb 2002
 AB Huntington's Disease is a genetic disorder leading to the degeneration of striatal-output neurons. Although no treatment is currently available for this disorder, many neurotrophic factors have been shown to increase the survival of striatal neurons. Intraventricular infusion of Glial cell line-Derived Neurotrophic Factor (GDNF) has been shown to be restorative for striatal neurons following Quinolinic Acid lesions in rodents. The present study investigated the neuroanatomical effects of **adeno-associated viral** delivery of the GDNF gene (AAV-GDNF) in a different rat model of Huntington's Disease. Two groups of Lewis rats received stereotaxic, bilateral injections of either AAV-GDNF (n=7) or AAV-Green Fluorescence Protein (AAV-GFP; n=7) into the striatum. One week later, rats were subcutaneously implanted with mini-**osmotic pumps** containing the mitochondrial toxin, 3-Nitropropionic Acid (40 mg/kg). All rats were sacrificed one week post-**osmotic pump** surgery. Histological analysis revealed that NeuN-immunoreactive striatal neurons were protected in rats treated with AAV-GDNF. Rats in the AAV-GDNF group exhibited significant increases in neuronal number (45%) and density (38%) in the striatum (p<.001) compared to rats treated with AAV-GFP. These data indicate that the viral-mediated transfer of the GDNF gene prevents the structural consequences of 3-NP lesion and may be a viable treatment for Huntington's Disease.

L4 ANSWER 10 OF 11 MEDLINE on STN DUPLICATE 2
 AN 2001176319 MEDLINE
 DN PubMed ID: 11144956
 TI Distribution of AAV-TK following intracranial convection-enhanced delivery into rats.
 AU Cunningham J; Oiwa Y; Nagy D; Podsakoff G; Colosi P; Bankiewicz K S
 CS Avigen, Inc., Alameda, CA, USA.
 SO Cell transplantation, (2000 Sep-Oct) 9 (5) 585-94.
 Journal code: 9208854. ISSN: 0963-6897.
 CY United States
 DT (EVALUATION STUDIES)
 Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 200103
 ED Entered STN: 20010404
 Last Updated on STN: 20010404
 Entered Medline: 20010329
 AB **Adeno-associated virus** (AAV)-based vectors are being tested in animal models as viable treatments for glioma and neurodegenerative disease and could potentially be employed to target a variety of central nervous system disorders. The relationship between dose of injected vector and its resulting distribution in brain tissue has not been previously reported nor has the most efficient method of delivery been determined. Here we report that convection-enhanced delivery (CED) of 2.5×10^8 , 2.5×10^9 , or 2.5×10^{10} particles of AAV-thymidine kinase (AAV-TK) into rat brain revealed a clear dose response. In the high-dose group, a volume of 300 mm³ of brain tissue was partially transduced. Results showed that **infusion pump** and

subcutaneous **osmotic pumps** were both capable of delivering vector via CED and that total particle number was the most important determining factor in obtaining efficient expression. Results further showed differences in histopathology between the delivery groups. While administration of vector using **infusion pump** had relatively benign effects, the use of **osmotic pumps** resulted in notable toxicity to the surrounding brain tissue. To determine tissue distribution of vector following intracranial delivery, PCR analysis was performed on tissues from rats that received high doses of AAV-TK. Three weeks following CED, vector could be detected in both hemispheres of the brain, spinal cord, spleen, and kidney.

L4 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
 AN 1998:55483 CAPLUS
 DN 128:97727
 TI Transformation and gene therapy of cells of the inner ear
 IN Lalwani, Anil; Schindler, Robert A.
 PA Regents of the University of California, USA; Lalwani, Anil; Schindler, Robert A.
 SO PCT Int. Appl., 66 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9800014	A1	19980108	WO 1997-US11602	19970627
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9735915	A1	19980121	AU 1997-35915	19970627
PRAI	US 1996-674231		19960628		
	WO 1997-US11602		19970627		

AB Compns. and methods are disclosed for transformation of cells of the inner ear and treatment of conditions of the inner ear using such methods. More specifically, cells of an inner ear of a subject are genetically altered to operatively incorporate a nucleotide sequence which expresses a gene product of interest (e.g., a therapeutic gene product). Preferably, the inner ear cell into which the DNA of interest is introduced and expressed is a cell of the cochlea, more preferably a cell of the spiral ligament, spiral limbus, stria vascularis, organ of Corti, spiral ganglion, and/or Reissner's membrane, and/or an auditory hair cell. The DNA of interest, preferably present within an **adeno-assocd.** **viral** vector, is introduced through a cannula inserted in the round or oval window and in communication with the perilymph or endolymph. Preferably, introduction of the DNA of interest is accomplished using an osmotic minipump.

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

=>